REMARKS

Claim 6 has been canceled without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the canceled claims in this or any other patent application. Accordingly, Claims 1-5 are presented for examination.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Information Disclosure Statement

The Examiner requested that Applicants provide further information regarding the BLAST results included in the Information Disclosure Statement submitted Sept. 5, 2002. Applicants submit herewith a new Information Disclosure Statement providing the accession numbers, publication date and sequences of the sequences identified in the BLAST search.

Applicants inadvertently listed U.S. Patent No. 5,546,637 on the Information Disclosure Statement rather than U.S. Patent No. 5,536,637. The Information Disclosure Statement submitted herewith includes U.S. Patent No. 5,536,637.

Priority

The Examiner asserts that the present application is entitled to priority only as of its filing date, May 2, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/090862 filed 6/26/1998.

Applicants submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility. The sequence of SEQ ID NO: 32 was first disclosed in

US Provisional Application 60/090862 filed 6/26/1998 in Figure 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Furthermore, as discussed below, Applicants maintain that the claimed antibodies have utility for the diagnosis of stomach tumors or lung tumors.

Rejections under 35 U.S.C. §101

The Examiner asserts that the claimed invention lacks a specific, substantial and credible utility. In particular, the Examiner asserts that the disclosure of the use of the claimed antibodies for identifying molecules that bind to PRO1115, diagnostic assays, affinity purification and therapeutic purposes does not meet the requirements of 35 U.S.C. §101. The Examiner asserts that there is no disclosure of the function of the protein and that the fact that the nucleic acid encoding PRO1115 is more highly expressed in normal stomach tissue or normal lung tissue relative to stomach tumors or lung tumors respectively does not impart utility because there is no evidence that the encoded polypeptide is more highly expressed in normal tissue.

The Examiner further asserts that the specification does not indicate the normal level of expression, does not indicate how high the expression level is compared to stomach tumor or lunch tumor and fails to describe the type of tumor. Finally, the Examiner asserts that the data in the specification was not corrected for aneuploidy.

As discussed in more detail below, Applicants maintain that, as provided in Example 18 of the application, the polypeptide of SEQ ID NO: 32 is more highly expressed in normal stomach tissue or normal lung tissue relative to stomach tumors or lung tumors and that this differential expression provides a specific, substantial and credible utility. Applicants further maintain that the data provided in the specification is indicative of mRNA levels, that it is not necessary to specify the particular type of tumor, and that it is not necessary to correct the data for aneuploidy

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." A

utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantially utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P., 2107 II(B)(1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the Applicant's assertions." (M.P.E.P. 2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must

establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Credible, Specific and Substantial Utility

Example 18 demonstrates that the nucleic acid encoding SEQ ID NO: 32 is expressed at a higher level in normal tissue than in stomach tumor or lung tumor respectively. Applicants maintain that this differential expression renders the claimed antibodies useful in diagnosing cancer.

The Examiner asserts that the specification does not indicate how high the expression level in normal tissue is relative to stomach tumor or lung tumor. Applicant notes that, as provided in the first Declaration of J. Christopher Grimaldi submitted herewith as Exhibit 1, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557, the level of nucleic acid encoding the polypeptide of SEQ ID NO: 32 in normal skin tissue is significantly higher than that in stomach tumor or lung tumor. The first Declaration of J. Christopher Grimaldi describes the techniques used to measure the level of nucleic acid encoding the polypeptide of SEQ ID NO: 32 in normal tissue and stomach tumor or lung tumor. As stated in Paragraph 6 of the first Declaration of J. Christopher Grimaldi, "Using the widely accepted technique of PCR, it was determined whether the polynucleotides tested were more highly expressed, less expressed, or whether expression remained the same in tumor tissue as compared to its normal counterpart. Because this technique relies on the visual detection of ethidium bromide staining of PCR products on agarose gels, it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA." In addition, in Paragraph 7 of the first Declaration, Mr. Grimaldi states that "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue. The precise type of tumor is also irrelevant; again, the assay was designed to indicate whether a difference exists between normal tissue and tumor tissue of the same type. If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." Thus, the antibodies

which bind polypeptide of SEQ ID NO: 32 are useful for diagnosing stomach tumor or lung tumor.

The Examiner also asserts that because the DNA was amplified from the cDNA library from different human tumor and human normal tissue samples, there is no possibility for direct comparison of the expression between the normal and tumor tissues. In paragraph 5 of Exhibit 1, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, "[a] slight amplification of a gene does not necessarily mean overexpression in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 6. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, Applicants fail to see how it is relevant to the utility of the disclosed polypeptides or their antibodies whether the differential expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the differential expression of the gene encoding the polypeptide of SEQ ID NO: 32 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal stomach tissue or normal lung tissue relative to stomach tumor or lung tumor respectively and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer. As discussed below, this fact leads to utility for the claimed antibodies.

The PTO argues that there is no supporting evidence that the polypeptide encoded by the nucleotide of the instant invention is more highly expressed in the normal tissue compared to the tumor tissue. The PTO also states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. Relying on Pennica *et al.*, 1998, PNAS USA 95:14717-14722 (hereinafter Pennica), the PTO states that the data pertaining to polynucleotides do not necessarily indicate anything significant regarding the claimed polypeptides.

Applicants respectfully submit that the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 7-8. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding the polypeptide of SEQ ID NO: 32 in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that

one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

The Examiner also asserts that the level of a nucleic acid encoding a polypeptide is not indicative of the level of the polypeptide itself. Applicants submit herewith a second Declaration of J. Christopher Grimaldi submitted herewith as Exhibit 2, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557. As stated in Paragraph 5 of the second Declaration of J. Christopher Grimaldi, "in the vast majority of cases, when a gene is over-expressed, as evidenced by an increased production of mRNA, the gene product or polypeptide will also be over-expressed...This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." Thus, the detection of higher levels of mRNA encoding the polypeptide of SEQ ID NO: 32 in normal tissue relative to stomach tumor or lung tumor is expected to result in higher polypeptide expression in normal tissue relative to stomach tumor or lung tumor respectively. Applicants further maintain that the particular type of tumor is irrelevant. In addition, Applicants maintain that whether the polypeptide is under-expressed in tumors as a result of aneuploidy or not is irrelevant. Rather Applicants maintain that regardless of the biological reason for under-expression, the claimed antibodies are useful for discriminating between normal and cancerous tissue and that this ability is sufficient to satisfy the requirements of 35 U.S.C. §101 and §112.

Scientists regularly rely on the results of gene expression to point the way to differential protein expression in disease and, in this case, cancer. Submitted herewith as Exhibit 3 is the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene

transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that based on the gene expression data for the nucleic acids encoding the polypeptide of SEQ ID NO: 32, the polypeptide of SEQ ID NO: 32 is concomitantly more highly expressed in normal stomach tissue or normal lung tissue relative to stomach tumor or lung tumor respectively.

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for the polypeptide of SEQ ID NO: 32, which Applicants submit is not true, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 4), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 5). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed antibodies.

The use of the PRO polypeptides to generate antibodies is disclosed in the specification at Paragraph [0361]-Paragraph [0396] and Paragraph [0493]-Paragraph [0499]. The use of antibodies against the PRO polypeptides as diagnostic tools is disclosed in the specification in Paragraph [0407].

The utility guidelines recognize that the diagnosis of cancer is a credible utility. (See page 5 of the Revised Interim Utility Guidelines Training Materials which provide that use as a diagnostic marker is a credible utility.)

Furthermore, the utility of the claimed antibodies as a stomach tumor or lung tumor diagnostic is specific to the claimed antibodies and is not a characteristic of antibodies in general.

Finally, stomach tumor or lung tumor diagnosis is a substantial utility. (See the caveat in Example 12 of the Revised Interim Utility Guidelines Training Materials, pages 69-70, which states that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin cells and antibodies against the protein can be used to diagnosis cancer.)

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

As discussed below, Applicants provide herewith several expert opinions supporting the utility of the present invention. Applicants submit that one of ordinary skill in the art would have no legitimate basis to doubt the credibility of the statements made by Mr. Grimaldi and Dr. Polakis and must treat as true the statements made by these experts. Applicants remind the Examiner that "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." PTO Utility Examination Guidelines (2001).

Applicants believe that they have met their burden of establishing a specific and substantial credible utility for the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §101 be withdrawn.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-6 were also rejected under the first paragraph of 35 U.S.C. §112. The Examiner asserts that since the claimed invention lacks utility one skilled in the art would be unable to use it. As discussed above, Applicants maintain that the claimed invention possesses a specific, substantial and credible utility. Accordingly, Applicants respectfully request that the rejection under under the first paragraph of 35 U.S.C. §112 be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claim 1 was rejected as being indefinite in the recitation that the claimed antibody "binds" the polypeptide of SEQ ID NO: 32. The PTO argues that specifically is not defined in the claims and the specification does not provide a standard for ascertaining the requisite degree of binding. The PTO also argues that because some level of specificity is implicit in all the claims, the difference between "binds" and "binds specifically" cannot be determined.

Claim 6 has been canceled and Claim 1 amended to recite "specifically binds". Applicants submit that the term "specifically binds" has a well established meaning – it refers to the binding of an antibody to a particular polypeptide, where the antibody does not substantially bind to any other polypeptide. One of skill in the art would readily understand the language of the claims to mean that the claimed antibodies bind to specifically defined polypeptides (in this case the polypeptides of SEQ ID NO: 32) but do not substantially bind to any other polypeptides. Since claim terms should be given their ordinary, art-recognized meaning, Applicants submit the present rejection is misplaced, and request that it be withdrawn.

Rejections under 35 U.S.C. §103

Claims 1-6 were rejected under 35 U.S.C. §103. The Examiner asserts that these claims are obvious over Collier,Accession No. Q9BWY7, June 2001 in view of Turner et al. Accession No. AAX146414 (WO 0134804A1, published May 2001). Applicants submit that because both of the cited references were published in 2001 they do not constitute prior art to the present application. In particular, as discussed above , the sequence of SEQ ID NO: 32 was first disclosed in US Provisional Application 60/090862 filed 6/26/1998 in Figure 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants

are entitled to a priority date of at least **August 24, 2000**. Because each of the cited references were published after the priority date of the present application, they are not available as prior art against the present application. Accordingly, Applicants request that the PTO reconsider and withdraw the rejection under 35 U.S.C. §103.

Conclusion

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 14, 2004

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